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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : A61K 38/16 — A2

(11) International Publication Number: WO 95/17904

(43) International Publication Date: 6 July 1995 (06.07.95)

(21) International Application Number: PCT/US94/14717

(22) International Filing Date: 16 December 1994 (16.12.94)

(30) Priority Data:
08/173,996 28 December 1993 (28.12.93) US

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(81) Designated States: AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, ES, FI, GB, HU, JP, KP, KR, KZ, LK, LU, LV, MG, MN, MW, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SK, UA, UZ, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published
Without international search report and to be republished upon receipt of that report.

(54) Title: BOTULINUM TOXINS FOR TREATING VARIOUS DISORDERS AND ASSOCIATED PAIN

(57) Abstract

The present invention provides a method for relieving pain, associated with muscle contractions, a composition and a method of treating conditions such as cholinergic controlled secretions including excessive sweating, lacrimation and mucus secretions and a method for treating smooth muscle disorders including, but not limited to, spasms in the sphincter of the cardiovascular arteriole, gastrointestinal system, urinary, gall bladder and rectum, which method comprises administering to the patient suffering from said disorder or condition a therapeutically effective amount of Botulinum toxin selected from the group consisting of Botulinum toxin types B, C, D, E, F and G.

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BOTULINUM TOXINS FOR TREATING VARIOUS DISORDERS AND ASSOCIATED PAIN

FIELD OF THE INVENTION

The present invention provides novel methods for treating various disorders and conditions, with Botulinum toxins. Importantly, the present invention provides methods useful in relieving pain related to muscle activity or contracture and therefore is of advantage in the treatment of, for example, muscle spasm such as Temporomandibular Joint Disease, low back pain, myofascial pain, pain related to spasticity and dystonia, as well as sports injuries, and pain related to contractures in arthritis.

BACKGROUND OF THE INVENTION

Heretofore, Botulinum toxins, in particular Botulinum toxin type A, has been used in the treatment of a number of neuromuscular disorders and conditions involving muscular spasm; for example, strabismus, blepharospasm, spasmodic torticollis (cervical dystonia), oromandibular dystonia and spasmodic dysphonia (laryngeal dystonia). The toxin binds rapidly and strongly to presynaptic cholinergic nerve terminals and inhibits the exocytosis of acetylcholine by decreasing the frequency of acetylcholine release. This results in local paralysis and hence relaxation of the muscle afflicted by spasm.

For one example of treating neuromuscular disorders, see U.S. Patent No. 5,053,005 to Borodic, which suggests treating curvature of the juvenile

spine, i.e., scoliosis, with an acetylcholine release inhibitor, preferably Botulinum toxin A.

For the treatment of strabismus with Botulinum toxin type A, see Elston, J.S., et al., *British Journal of Ophthalmology*, 1985, 69, 718-724 and 891-896. For the treatment of blepharospasm with Botulinum toxin type A, see Adenis, J.P., et al., *J. Fr. Ophthalmol.*, 1990, 13 (5) at pages 259-264. For treating squint, see Elston, J.S., *Eye*, 1990, 4(4):VII. For treating spasmodic and oromandibular dystonia torticollis, see Jankovic et al., *Neurology*, 1987, 37, 616-623.

Spasmodic dysphonia has been treated with Botulinum toxin type A. See Blitzer et al., *Ann. Otol. Rhino. Laryngol*, 1985, 94, 591-594. Lingual dystonia was treated with Botulinum toxin type A according to Brin et al., *Adv. Neurol.* (1987) 50, 599-608. Finally, Cohen et al., *Neurology* (1987) 37 (Suppl. 1), 123-4, discloses the treatment of writer's cramp with Botulinum toxin type A.

The term Botulinum toxin is a generic term embracing the family of toxins produced by the anaerobic bacterium *Clostridium botulinum* and, to date, seven immunologically distinct neurotoxins have been identified. These have been given the designations A, B, C, D, E, F and G. For further information concerning the properties of the various Botulinum toxins, reference is made to the article by Jankovic and Brin, *The New England Journal of Medicine*, No. 17, 1990, pp. 1186-1194, and to the review by Charles L. Hatheway in Chapter 1 of the book entitled *Botulinum Neurotoxin and Tetanus Toxin*, L. L. Simpson, Ed.,

published by Academic Press Inc. of San Diego, California, 1989, the disclosures in which are incorporated herein by reference.

The neurotoxic component of Botulinum toxin has a molecular weight of about 150 kilodaltons and is thought to comprise a short polypeptide chain of about 50 kD which is considered to be responsible for the toxic properties of the toxin, i.e., by interfering with the exocytosis of acetylcholine, by decreasing the frequency of acetylcholine release, and a larger polypeptide chain of about 100 kD which is believed to be necessary to enable the toxin to bind to the pre-synaptic membrane.

The "short" and "long" chains are linked together by means of a simple disulfide bridge. (It is noted that certain serotypes of Botulinum toxin, e.g., type E, may exist in the form of a single chain un-nicked protein, as opposed to a dichain. The single chain form is less active but may be converted to the corresponding dichain by nicking with a protease, e.g., trypsin. Both the single and the dichain are useful in the method of the present invention.)

In general, four physiologic groups of *C. botulinum* are recognized (I, II, III, IV). The organisms capable of producing a serologically distinct toxin may come from more than one physiological group. For example, Type B and F toxins can be produced by strains from Group I or II. In addition, other strains of clostridial species (*C. baratii*, type F; *C. butyricum*, type E; *C. novyi*, type C_1 or D) have been identified which can produce botulinum neurotoxins.

Immunotoxin conjugates of ricin and antibodies, which are characterized as having enhanced cytotoxicity through improving cell surface affinity, are disclosed in European Patent Specification 0 129 434. The inventors note that botulinum toxin may be utilized in place of ricin.

Botulinum toxin is obtained commercially by establishing and growing cultures of *C. botulinum* in a fermenter and then harvesting and purifying the fermented mixture in accordance with known techniques.

Botulinum toxin type A, the toxin type generally utilized in treating neuromuscular conditions, is currently available commercially from several sources; for example, from Porton Products Ltd. UK, under the trade name "DYSPORT," and from Allergan, Inc., Irvine, California, under the trade name BOTOX®.

It is one object of the invention to provide novel treatments of neuromuscular disorders and conditions with various Botulinum toxin types. It is another object of the present invention to relieve pain with various Botulinum toxin types.

SUMMARY OF THE INVENTION

The present invention provides a method for relieving pain, associated with muscle contractions, a composition and a method of treating conditions such as cholinergic controlled secretions including excessive sweating, lacrimation and mucus secretions and a method for treating smooth muscle disorders including, but not limited to, spasms in the sphincter

of the cardiovascular arteriole, gastrointestinal system, urinary, gall bladder and rectum, which method comprises administering to the patient suffering from said disorder or condition a therapeutically effective amount of Botulinum toxin selected from the group consisting of Botulinum toxin types B, C, D, E, F and G.

Each serotype of Botulinum toxin has been identified as immunologically different proteins through the use of specific antibodies. For example, if the antibody (antitoxin) recognizes, that is, neutralizes the biological activity of, for example, type A it will not recognize types B,C,D, E, F or G.

While all of the Botulinum toxins appear to be zinc endopeptidases, the mechanism of action of different serotypes, for example, A and E within the neuron appear to be different than that of Type B. In addition, the neuronal surface "receptor" for the toxin appears to be different for the serotypes.

In the area of use of the Botulinum toxins in accordance with the present invention with regard to organ systems which involve the release of neurotransmitter, it is expected to introduce the toxins A, B, C, D, E, F, and G directly by local injections.

DETAILED DESCRIPTION

The Botulinum toxins used according to the present invention are Botulinum toxins type A, B, C, D, E, F and G.

The physiologic groups of *Clostridium botulinum* types are listed in Table I.

Table I. Physiologic Groups of *Clostridium botulinum*

Group	Toxin Sero-Type	Biochemistry	Milk Digest	Glucose Fermentation	Lipase	Phages & Plasmids	Phenotypically Related Clostridium (nontoxigenic)
I	A,B,F	proteolytic saccharolytic	+	+	+	+	C. sporogenes
II	B,E,F	nonproteolytic saccharolytic psychotrophic	-	+	+	+	
III	C,D	nonproteolytic saccharolytic	+	+	+	+	C. novyi
IV	G	proteolytic nonsaccharolytic	+	-	-	-	C. subterminale

These toxin types may be produced by selection from the appropriate physiologic group of *Clostridium botulinum* organisms. the organisms designated as Group I are usually referred to as proteolytic and produce Botulinum toxins of types A, B and F. The organisms designated as Group II are saccharolytic and produce Botulinum toxins of types B, E and F. The organisms designated as Group III produce only Botulinum toxin types C and D and are distinguished from organisms of Groups I and II by the production of significant amounts of propionic acid. Group IV organisms only produce neurotoxin of type G. The production of any and all of the Botulinum toxin types A, B, C, D, E, F and G are described in Chapter 1 of *Botulinum Neurotoxin and Tetanus Toxin*, cited above, and/or the references cited therein. Botulinum toxins types B, C, D, E, F and G are also available from various species of clostridia.

Currently fourteen species of clostridia are considered pathogenic. Most of the pathogenic strains produce toxins which are responsible for the various pathological signs and symptoms. Organisms which pro-

duce Botulinum toxins have been isolated from botulism outbreaks in humans (types A, B, E and F) and animals (types C and D). Their identities were described through the use of specific antitoxins (antibodies) developed against the earlier toxins. Type G toxin was found in soil and has low toxigenicity. However, it has been isolated from autopsy specimens, but thus far there has not been adequate evidence that type G botulism has occurred in humans.

Preferably, the toxin is administered by means of intramuscular injection directly into a local area such as a spastic muscle, preferably in the region of the neuromuscular junction, although alternative types of administration (e.g., subcutaneous injection), which can deliver the toxin directly to the affected region, may be employed where appropriate. The toxin can be presented as a sterile pyrogen-free aqueous solution or dispersion and as a sterile powder for reconstitution into a sterile solution or dispersion.

Where desired, tonicity adjusting agents such as sodium chloride, glycerol and various sugars can be added. Stabilizers such as human serum albumin may also be included. The formulation may be preserved by means of a suitable pharmaceutically acceptable preservative such as a paraben, although preferably it is unpreserved.

It is preferred that the toxin is formulated in unit dosage form; for example, it can be provided as a sterile solution in a vial or as a vial or sachet containing a lyophilized powder for reconstituting a suitable vehicle such as saline for injection.

In one embodiment, the Botulinum toxin is formulated in a solution containing saline and pasteurized human serum albumin, which stabilizes the toxin and minimizes loss through non-specific adsorption. The solution is sterile filtered (0.2 micron filter), filled into individual vials and then vacuum-dried to give a sterile lyophilized powder. In use, the powder can be reconstituted by the addition of sterile unpreserved normal saline (sodium chloride 0.9% for injection).

The dose of toxin administered to the patient will depend upon the severity of the condition; e.g., the number of muscle groups requiring treatment, the age and size of the patient and the potency of the toxin. The potency of the toxin is expressed as a multiple of the LD_{50} value for the mouse, one unit (U) of toxin being defined as being the equivalent amount of toxin that kills 50% of a group of 18 to 20 female Swiss-Webster mice, weighing about 20 grams each.

The dosages used in human therapeutic applications are roughly proportional to the mass of muscle being injected. Typically, the dose administered to the patient may be up from about 0.01 to about 1,000 units; for example, up to about 500 units, and preferably in the range from about 80 to about 460 units per patient per treatment, although smaller of larger doses may be administered in appropriate circumstances such as up to about 50 units for the relief of pain and in controlling cholinergic secretions.

As the physicians become more familiar with the use of this product, the dose may be changed. In the Botulinum toxin type A, available from Porton,

DYSPORT, 1 nanogram (ng) contains 40 units. 1 ng of the Botulinum toxin type A, available from Allergan, Inc., i.e., BOTOX®, contains 4 units. The potency of Botulinum toxin and its long duration of action mean that doses will tend to be administered on an infrequent basis. Ultimately, however, both the quantity of toxin administered and the frequency of its administration will be at the discretion of the physician responsible for the treatment and will be commensurate with questions of safety and the effects produced by the toxin.

In some circumstances, particularly in the relief of pain associated with sports injuries, such as, for example, charleyhorse, botulinum type F, having a short duration activity, is preferred.

The invention will now be illustrated by reference to the following nonlimiting examples.

In each of the examples, appropriate areas of each patient are injected with a sterile solution containing the confirmation of Botulinum toxin. Total patient doses range from about 0.01 units to 460 units. Before injecting any muscle group, careful consideration is given to the anatomy of the muscle group, the aim being to inject the area with the highest concentration of neuromuscular junctions, if known. Before injecting the muscle, the position of the needle in the muscle is confirmed by putting the muscle through its range of motion and observing the resultant motion of the needle end. General anaesthesia, local anaesthesia and sedation are used according to the age of the patient, the number of sites to be injected, and the particular needs of the

patient. More than one injection and/or sites of injection may be necessary to achieve the desired result. Also, some injections, depending on the muscle to be injected, may require the use of fine, hollow, teflon-coated needles, guided by electromyography.

Following injection, it is noted that there are no systemic or local side effects and none of the patients are found to develop extensive local hypotonicity. The majority of patients show an improvement in function both subjectively and when measured objectively.

Example 1
The Use of Botulinum toxin Type in the Treatment of Tardive Dyskinesia

A male patient, age 45, suffering from tardive dyskinesia resulting from the treatment with an antipsychotic drug, such as Thorazine or Haldol, is treated with 150 units of Botulinum toxin type B by direct injection of such toxin into the facial muscles. After 1-3 days, the symptoms of tardive dyskinesia, i.e., orofacial dyskinesia, athetosis, dystonia, chorea, tics and facial grimacing, etc. are markedly reduced.

Example 1(a)

The method of Example 1 is repeated, except that a patient suffering from tardive dyskinesia is injected with 50-200 units of Botulinum toxin type C. A similar result is obtained.

Example 1(b)

The method of Example 1 is repeated, except that a patient suffering from tardive dyskinesia is injected with 50-200 units of Botulinum toxin type D. A similar result is obtained.

Example 1(c)

The method of Example 1 is repeated, except that a patient suffering from tardive dyskinesia is injected with 50-200 units of Botulinum toxin type E. A similar result is obtained.

Example 1(d)

The method of Example 1 is repeated, except that a patient suffering from tardive dyskinesia is injected with 50-200 units of Botulinum toxin type F. A similar result is obtained.

Example 1(e)

The method of Example 1 is repeated, except that a patient suffering from tardive dyskinesia is injected with 50-200 units of Botulinum toxin type G. A similar result is obtained.

Example 2

The Use of Botulinum toxin Type B in the Treatment of Spasmodic Torticollis

A male, age 45, suffering from spasmodic torticollis, as manifested by spasmodic or tonic contractions of the neck musculature, producing

stereotyped abnormal deviations of the head, the chin being rotated to one side, and the shoulder being elevated toward the side at which the head is rotated, is treated by injection with 100-1,000 units of Botulinum toxin type E. After 3-7 days, the symptoms are substantially alleviated; i.e., the patient is able to hold his head and shoulder in a normal position.

Example 2(a)

The method of Example 2 is repeated, except that a patient suffering from spasmodic torticollis is injected with 100-1,000 units of Botulinum toxin type B. A similar result is obtained.

Example 2(b)

The method of Example 2 is repeated, except that a patient suffering from spasmodic torticollis is injected with 100-1,000 units of Botulinum toxin type C. A similar result is obtained.

Example 2(c)

The method of Example 2 is repeated, except that a patient suffering from spasmodic torticollis is injected with 100-1,000 units of Botulinum toxin type D. A similar result is obtained.

Example 2(d)

The method of Example 2 is repeated, except that a patient suffering from spasmodic torticollis is

injected with 100-1,000 units of Botulinum toxin type E. A similar result is obtained.

Example 2(e)

The method of Example 2 is repeated, except that a patient suffering from spasmodic torticollis is injected with 100-1,000 units of Botulinum toxin type F. A similar result is obtained.

Example 2(f)

The method of Example 2 is repeated, except that a patient suffering from spasmodic torticollis is injected with 100-1,000 units of Botulinum toxin type G. A similar result is obtained.

Example 3
The Use of Botulinum toxin in the Treatment of Essential Tremor

A male, age 45, suffering from essential tremor, which is manifested as a rhythmical oscillation of head or hand muscles and is provoked by maintenance of posture or movement, is treated by injection with 50-1,000 units of Botulinum toxin type B. After two to eight weeks, the symptoms are substantially alleviated; i.e., the patient's head or hand ceases to oscillate.

Example 3(a)

The method of Example 3 is repeated, except that a patient suffering from essential tremor is injected with 100-1,000 units of Botulinum toxin type C. A similar result is obtained.

Example 3(b)

The method of Example 3 is repeated, except that a patient suffering from essential tremor is injected with 100-1,000 units of Botulinum toxin type D. A similar result is obtained.

Example 3(c)

The method of Example 3 is repeated, except that a patient suffering from essential tremor is injected with 100-1,000 units of Botulinum toxin type E. A similar result is obtained.

Example 3(d)

The method of Example 3 is repeated, except that a patient suffering from essential tremor is injected with 100-1,000 units of Botulinum toxin type F. A similar result is obtained.

Example 3(e)

The method of Example 3 is repeated, except that a patient suffering from essential tremor is injected with 100-1,000 units of Botulinum toxin type G. A similar result is obtained.

Example 4
The Use of Botulinum toxin in the Treatment of Spasmodic Dysphonia

A male, age 45, unable to speak clearly, due to spasm of the vocal chords, is treated by injection of the vocal chords with Botulinum toxin type B, having an activity of 80-500 units. After 3-7 days, the patient is able to speak clearly.

Example 4(a)

The method of Example 4 is repeated, except that a patient suffering from spasmodic dysphonia is injected with 80-500 units of Botulinum toxin type C. A similar result is obtained.

Example 4(b)

The method of Example 4 is repeated, except that a patient suffering from spasmodic dysphonia is injected with 80-500 units of Botulinum toxin type D. A similar result is obtained.

Example 4(c)

The method of Example 4 is repeated, except that a patient suffering from spasmodic dysphonia is injected with 80-500 units of Botulinum toxin type E. A similar result is obtained.

Example 4(d)

The method of Example 4 is repeated, except that a patient suffering from spasmodic dysphonia is

injected with 80-500 units of Botulinum toxin type F. A similar result is obtained.

Example 4(e)

The method of Example 4 is repeated, except that a patient suffering from spasmodic dysphonia is injected with 8-500 units of Botulinum toxin type G. A similar result is obtained.

Example 5

The Use of Botulinum toxin Types A-G in the Treatment of Excessive Sweating, Lacrimation or Mucus Secretion or Other Cholinergic Controlled Secretions

A male, age 65, with excessive unilateral sweating is treated by administering 0.01 to 50 units, of Botulinum toxin, depending upon degree of desired effect. The larger the dose, usually the greater spread and duration of effect. Small doses are used initially. Any serotype toxin alone or in combination could be used in this indication. The administration is to the gland nerve plexus, ganglion, spinal cord or central nervous system to be determined by the physician's knowledge of the anatomy and physiology of the target glands and secretary cells. In addition, the appropriate spinal cord level or brain area can be injected with the toxin (although this would cause many effects, including general weakness). Thus, the gland (if accessible) or the nerve plexus or ganglion are the targets of choice. Excessive sweating, tearing (lacrimation), mucus secretion or gastrointestinal secretions are positively influenced by the cholinergic nervous system. Sweating and

tearing are under greater cholinergic control than mucus or gastric secretion and would respond better to toxin treatment. However, mucus and gastric secretions could be modulated through the cholinergic system. All symptoms would be reduced or eliminated with toxin therapy in about 1-7 days. Duration would be weeks to several months.

Example 6

The Use of Botulinum toxin Types A-G in the Treatment of Muscle Spasms in Smooth Muscle Disorders Such As Sphincters of the Cardiovascular Arteriole, Gastrointestinal System, Urinary or Gall Bladder, Rectal, Etc.

A male, age 30-40, with a constricted pyloric valve which prevents his stomach from emptying, is treated by administering 1-50 units of Botulinum toxin. The administration is to the pyloric valve (which controls release of stomach contents into the intestine) divided into 2 to 4 quadrants, injections made with any endoscopic device or during surgery. In about 1-7 days, normal emptying of the stomach, elimination or drastic reduction in regurgitation occurs.

Example 7

The Use of Botulinum toxin Types A-G in the Treatment of Muscle Spasms and Control of Pain Associated With Muscle Spasms in Temporal Mandibular Joint Disorders

A female, age 35, is treated by administration of 0.1 to 50 units total of Botulinum toxin. The administration is to the muscles controlling the

closure of the jaw. Overactive muscles may be identified with EMG (electromyography) guidance. Relief of pain associated with muscle spasms, possible reduction in jaw clenching occurs in about 1-3 days.

Example 8

The Use of Botulinum toxin Types A-G in the Treatment of Muscle Spasms and Control of Pain Associated with Muscle Spasms in Conditions Secondary to Sports Injuries (Charleyhorse)

A male, age 20, with severe cramping in thigh after sports injury is treated by administration of a short duration toxin, possible low dose (0.1-25 units) of preferably type F to the muscle and neighboring muscles which are in contraction ("cramped"). Relief of pain occurs in 1-7 days.

Example 9

The Use of Botulinum toxin Types A-G in the Treatment of Muscle Spasms and Control of Pain Associated with Muscle Spasms in Smooth Muscle Disorders Such as Gastrointestinal Muscles

A female, age 35, with spastic colitis, is treated with 1-100 units of Botulinum toxin divided into several areas, enema (1-5 units) delivered in the standard enema volume, titrate dose, starting with the lowest dose. Injection is to the rectum or lower colon or a low dose enema may be employed. Cramps and pain associated with spastic colon are relieved in 1-10 days.

Example 9

The Use of Botulinum toxin Types A-G in the Treatment of Muscle Spasms and Control of Pain Associated with Muscle Spasms in Spasticity Conditions Secondary to Stroke, Traumatic Brain or Spinal Cord Injury

A male, age 70, post-stroke or cerebral vascular event, is injected with 50 to 300 units of Botulinum toxin in the major muscles involved in severe closing of hand and curling of wrist and forearm or the muscles involved in the closing of the legs such that the patient and attendant have difficulty with hygiene. Relief of these symptoms occurs in 7 to 21 days.

Example 10

The Use of Botulinum toxin Types A-G in the Treatment of Patients with Swallowing disorders

A patient with a swallowing disorder caused by excessive throat muscle spasms is injected with about 1 to about 300 units of Botulinum toxin in the throat muscles. Relief the swallowing disorder occurs in about 7 to about 21 days.

Example 11

The Use of Botulinum toxin Types A-G in the Treatment of Patients with Tension Headache

A patient with a tension headache caused by excessive throat muscle spasms is injected with about 1 to about 300 units of Botulinum toxin in muscles of the head and upper neck. Relief the tension headache occurs in about 1 to about 7 days.

Although there has been hereinabove described a use of Botulinum toxins for treating various disorders, conditions and pain, in accordance with the present invention, for the purpose of illustrating the manner in which the invention may be used to advantage, it should be appreciated that the invention is not limited thereto since many obvious modifications can be made, and it is intended to include within this invention any such modifications as will fall within the scope of the appended claims. Accordingly, any and all modifications, variations, or equivalent arrangements which may occur to those skilled in the art, should be considered to be within the scope of the present invention as defined in the appended claims.

WHAT IS CLAIMED IS:

1. A method of treating cholinergic controlled secretions including excessive sweating, lacrimation and mucus secretion, said method comprising administering to the patient a therapeutically effective amount of Botulinum toxin type A in order to reduce the secretion.

2. The method according to claim 1 wherein the Botulinum toxin type A is administered to the patient's nerve plexus in an amount of between about 0.01 and about 50 units.

3. The method according to claim 1 wherein the Botulinum toxin type A is administered to the patient's ganglion in an amount of between about 0.01 and about 50 units.

4. The method according to claim 1 wherein the Botulinum toxin type A is administered to the patient's spinal cord in an amount of between about 0.01 and about 50 units.

5. The method according to claim 1 wherein the Botulinum toxin type A is administered to the patient's central nervous system in an amount of between about 0.01 and about 50 units.

6. A method for relieving pain associated with smooth muscle disorders, including spasms in the sphincters of the cardiovascular arteriole, gastrointestinal system, urinary, gall bladder and rectum, said method comprising administering to the patient a

therapeutically effective amount of Botulinum toxin type A in order to relieve pain.

7. The method according to claim 6 wherein the Botulinum toxin type A is administered to the patient's pyloric valve in an amount between about 1 and about 50 units.

8. A method for treating smooth muscle disorders, including spasms in the sphincters of the cardiovascular arteriole, gastrointestinal system, urinary, gall bladder and rectum, said method comprising administering to the patient a therapeutically effective amount of Botulinum toxin type A in order to lessen the spasms.

9. The method according to claim 8 wherein the Botulinum toxin type A is administered to the patient's pyloric valve in an amount between about 1 and about 50 units.

10. A method for relieving pain associated with smooth muscle disorders, including spasms in the lower gastrointestinal muscles and rectum, said method comprising administering to the patient a therapeutically effective amount of Botulinum toxin type A in order to relieve pain.

11. The method according to claim 10 wherein the Botulinum toxin type A is administered to the patient's lower colon in an amount between about 0.01 and about 50 units.

12. A method for relieving pain associated with smooth muscle disorders, including spasms in the

sphincters lower gastrointestinal muscles and rectum, said method comprising administering to the patient a therapeutically effective amount of Botulinum toxin type A in order to lessen the spasms.

13. The method according to claim 12 wherein the Botulinum toxin type A is administered to the patient's lower colon in an amount between about 0.01 and about 50 units.

14. A method for relieving pain associated with muscle spasms in conditions secondary to sports injuries, said method comprising administering to a patient a therapeutically effective amount of a Botulinum toxin of a type having short duration activity in order to relieve pain.

15. The method according to claim 14 wherein the Botulinum toxin comprises Botulinum toxin type F.

16. The method according to claim 15 wherein the therapeutic amount comprises a dose of between about 1 and about 10 units.

17. The method according to claim 16 wherein the muscle spasms occur in a patient's thigh and the Botulinum toxin is administered into the thigh

18. A method for relieving pain associated with contractions in arthritis, said method comprising administering to a patient a therapeutically effective amount of a Botulinum toxin in order to relieve pain.

19. A method for treating swallowing disorders, including spasms, said method comprising administering

to the patient a therapeutically effective amount of Botulinum toxin type A.

10

20. A method for treating tension headache comprising administering to the patient a therapeutically effective amount of Botulinum toxin type A.

INTERNATIONAL SEARCH REPORT

Interna J Application No
PCT/US 94/14717

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K38/16

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	EXPERIENTIA, vol.33, no.6, 15 June 1977 pages 750 - 751 KONDO T., ET AL. 'Modification of the action of pentagastrin on acid secretion by botulinum toxin' * see the whole document * ---	1
Y	SCHWEIZ. MED. WSCHR., vol.104, pages 685 - 693 G. JENZER ET AL. 'Botulismus Typ B' * see the summary, Page 690, Figure 6 and left column, ultimate paragraph * --- -/--	1

[X] Further documents are listed in the continuation of box C.

[ ] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
27 April 1995	15. 09. 95

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax (+ 31-70) 340-3016	ISERT B.

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	NEW SCIENTIST, no.1746, 8 December 1990 page 24 N. HENESON 'Deadly toxin calms excited muscles' * see the whole article * ---	1
A	ARCH. OPHTHALMOL., vol.103, 5 pages 1305 - 1306 SAVINO P.J., ET AL 'hemifacial spasm treated with botulinum A toxin injection' * see the abstract * ---	1
A	EUR. NEUROL., vol.33, pages 199 - 203 D. BOGHEN ET AL. 'Effectiveness of Botulinum toxin in the treatment of spasmodic torticollis' * see the abstract * -----	1

3

INTERNATIONAL SEARCH REPORT

In. ational application No.
PCT/US 94/ 14717

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

- claims 1-5
- claims 6-13
- claims 14-20

- See (1) additional sheet PCT/ISA/210

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1-5

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/210

LACK OF UNITY OF INVENTION

1. Claims: 1-5 Method for treating cholinergic secretions using Botulinum toxin

2. Claims: 6-13 Method for treating smooth muscle disorders and pain associated therewith using Botulinum toxin

3. Claims: 14-20 Method for treating spastic muscle disorders and pain associated therewith using Botulinum toxin

The present application lacks unity of invention since it describes 3 different subjects defined below which are not linked by a common novel and inventive concept.

The separate inventions/groups of invention are:

A.) Claims 1-5 Method for treating cholinergic secretions using Botulinum toxin

B.) Claims 6-13 Method for treating smooth muscle disorders and pain associated therewith using Botulinum toxin

C.) Claims 14-20 Method for treating spastic muscle disorders and pain associated therewith using Botulinum toxin

(See also page 4 line 29 - page 5 line 7 of the application.)

It is to be noted the use of Botulinum toxins for treating diseases, especially those included in the above groups B) and C) is known as acknowledged in the description at pages 1-3. See also D. Boghen and M. Flanders, Eur. Neurol., 1993, Vol. 33, p. 199-203, which describes the effectiveness of Botulinum toxin in the treatment of spasmodic torticollis and associated pain.

S2 1 PN=EP 194276

2/39/1
DIALOG(R)File 345:Inpadoc/Fam.& Legal Stat.

5920758
Basic Patent (No,Kind,Date): GB 8422238 A0 841010 <No. of Patents: 011>
Patent Family:

Patent No	Kind	Date	Applic No	Kind	Date	
AT 92959	E	930815	EP 85904274	A	850903	
DE 3587524	C0	930916	EP 85904274	A	850903	
DE 3587524	T2	940120	EP 85904274	A	850903	
EP 194276	A1	860917	EP 85904274	A	850903	
EP 194276	B1	930811	EP 85904274	A	850903	
GB 8422238	A0	841010	GB 8422238	A	840903	(BASIC)
GB 8608827	A0	860514	GB 868827	A	860411	
GB 2177096	A1	870114	GB 868827	A	860411	
GB 2177096	B2	890517	GB 868827	A	860411	
JP 62500352	T2	870219	JP 85503940	A	850903	
WO 8601533	A1	860313	WO 85GB392	A	850903	

Priority Data (No,Kind,Date):
EP 85904274 A 850903
GB 8422238 A 840903
WO 85GB392 A 850903
WO 85GB392 W 850903
PATENT FAMILY:
AUSTRIA (AT)
Patent (No,Kind,Date): AT 92959 E 930815
HERSTELLUNG VON CHIMAEREN ANTIKOERPERN. (German)
Patent Assignee: CELLTECH LTD (GB)
Author (Inventor): NEUBERGER MICHAEL SAMUEL; RABBITTS TERENCE HOWARD
Priority (No,Kind,Date): EP 85904274 A 850903; GB 8422238 A 840903; WO 85GB392 A 850903
Applic (No,Kind,Date): EP 85904274 A 850903
Addnl Info: 00194276 930811
IPC: * C12N-015/13; C12N-015/62; A61K-039/395; C12P-021/00; G01N-033/563
CA Abstract No: * 105(05)036846F
Derwent WPI Acc No: * C 86-081635
Language of Document: English

AUSTRIA (AT)
Legal Status (No,Type,Date,Code,Text):

AT 92959	R	930815	AT REF	CORRESPONDS TO EP-PATENT (ENTSPRICHT EP-PATENT) EP 194276 P 930811
AT 92959	R	940215	AT UEP	PUBLICATION OF TRANSLATION OF EUROPEEN PATENT SPECIFICATION (UEBERSETZUNG DER EUROPAEISCHEN PATENTSCHRIFT AUSGEGEBEN)

GERMANY (DE)

Patent (No,Kind,Date): DE 3587524 C0 930916
HERSTELLUNG VON CHIMAEREN ANTIKOERPERN. (German)
Patent Assignee: CELLTECH LTD (GB)
Author (Inventor): NEUBERGER MICHAEL (GB); RABBITTS TERENCE (GB)
Priority (No,Kind,Date): WO 85GB392 W 850903; GB 8422238 A 840903
Applic (No,Kind,Date): EP 85904274 A 850903
IPC: * C12N-015/13; C12N-015/62; A61K-039/395; C12P-021/00; G01N-033/563
CA Abstract No: * 105(05)036846F
Derwent WPI Acc No: * C 86-081635
Language of Document: German
Patent (No,Kind,Date): DE 3587524 T2 940120
HERSTELLUNG VON CHIMAEREN ANTIKOERPERN. (German)
Patent Assignee: CELLTECH LTD (GB)
Author (Inventor): NEUBERGER MICHAEL (GB); RABBITTS TERENCE (GB)
Priority (No,Kind,Date): WO 85GB392 W 850903; GB 8422238 A 840903
Applic (No,Kind,Date): EP 85904274 A 850903
IPC: * C12N-015/13; C12N-015/62; A61K-039/395; C12P-021/00; G01N-033/563
CA Abstract No: * 105(05)036846F
Derwent WPI Acc No: * C 86-081635
Language of Document: German

GERMANY (DE)
Legal Status (No,Type,Date,Code,Text):
DE 3587524 P 930916 DE REF CORRESPONDS TO (ENTSPRICHT) EP 194276 P 930916
DE 3587524 P 940120 DE 8373 TRANSLATION OF PATENT DOCUMENT OF EUROPEAN PATENT WAS RECEIVED AND HAS BEEN PUBLISHED (UEBERSETZUNG DER PATENTSCHRIFT DES EUROPAEISCHEN PATENTES IST EINGEGANGEN UND VEROEFFENTLICHT WORDEN)
DE 3587524 P 940811 DE 8363 OPPOSITION AGAINST THE PATENT (EINSPRUCH GEGEN DAS PATENT ERHOBEN)

EUROPEAN PATENT OFFICE (EP)
Patent (No,Kind,Date): EP 194276 A1 860917
PRODUCTION OF CHIMERIC ANTIBODIES (English; French; German)
Patent Assignee: CELLTECH LTD (GB)
Author (Inventor): NEUBERGER MICHAEL SAMUEL; RABBITTS TERENCE HOWARD
Priority (No,Kind,Date): GB 8422238 A 840903; WO 85GB392 W 850903
Applic (No,Kind,Date): EP 85904274 A 850903
Designated States: (National) AT; BE; CH; DE; FR; GB; IT; LI; LU; NL; SE
IPC: * C12N-015/00; C07K-015/00; A61K-039/395; C07K-003/18; C12N-005/00; C12P-021/00; G01N-033/563
Language of Document: English
Patent (No,Kind,Date): EP 194276 B1 930811
PRODUCTION OF CHIMERIC ANTIBODIES (English; French; German)
Patent Assignee: CELLTECH LTD (GB)
Author (Inventor): NEUBERGER MICHAEL SAMUEL (GB); RABBITTS TERENCE

HOWARD (GB)
Priority (No,Kind,Date): WO 85GB392 W 850903; GB 8422238 A 840903
Applic (No,Kind,Date): EP 85904274 A 850903
Designated States: (National) AT; BE; CH; DE; FR; GB; IT; LI; LU; NL; SE
IPC: * C12N-015/13; C12N-015/62; A61K-039/395; C12P-021/00; G01N-033/563
CA Abstract No: * 105(05)036846F
Derwent WPI Acc No: * C 86-081635
Language of Document: English

EUROPEAN PATENT OFFICE (EP)
Legal Status (No,Type,Date,Code,Text):

EP 194276 P 840903 EP AA PRIORITY (PATENT APPLICATION) (PRIORITAET (PATENTANMELDUNG))
GB 8422238 A 840903

EP 194276 P 850903 EP AA PCT-APPLICATION (PCT-ANMELDUNG)
WO 85GB392 W 850903

EP 194276 P 850903 EP AE EP-APPLICATION (EUROPAEISCHE ANMELDUNG)
EP 85904274 A 850903

EP 194276 P 860917 EP AK DESIGNATED CONTRACTING STATES IN AN APPLICATION WITH SEARCH REPORT (IN EINER ANMELDUNG BENANNTE VERTRAGSSTAATEN)
AT BE CH DE FR GB IT LI LU NL SE

EP 194276 P 860917 EP A1 PUBLICATION OF APPLICATION WITH SEARCH REPORT (VEROEFFENTLICHUNG DER ANMELDUNG MIT RECHERCHENBERICHT)

EP 194276 P 860917 EP 17P REQUEST FOR EXAMINATION FILED (PRUEFUNGSANTRAG GESTELLT)
860418

EP 194276 P 880706 EP 17Q FIRST EXAMINATION REPORT (ERSTER PRUEFUNGSBESCHEID)
880520

EP 194276 P 930811 EP AK DESIGNATED CONTRACTING STATES MENTIONED IN A PATENT SPECIFICATION (IN EINER PATENTSCHRIFT ANGEFUEHRTE BENANNTE VERTRAGSSTAATEN)
AT BE CH DE FR GB IT LI LU NL SE

EP 194276 P 930811 EP B1 PATENT SPECIFICATION (PATENTSCHRIFT)

EP 194276 P 930811 EP REF IN AUSTRIA REGISTERED AS: (IN AT EINGETRAGEN ALS:)
AT 92959 R 930815

EP 194276 P 930916 EP REF CORRESPONDS TO: (ENTSPRICHT)
DE 3587524 P 930916

EP 194276 P 930917 EP ET FR: TRANSLATION FILED (FR: TRADUCTION A ETE REMISE)

EP 194276 P 930917 EP ITF IT: TRANSLATION FOR A EP PATENT FILED (IT: DEPOSITO TRADUZIONE DI BREVETTO EUROPEO)
STUDIO TORTA SOCIETA' SEMPLICE

EP 194276 P 931213 EP EPTA LU: LAST PAID ANNUAL FEE (LU: DERNIER PAYEMENT D'UNE TAXE ANNUELE)
EP 194276 P 940706 EP 26 OPPOSITION FILED (EINSPRUCH EINGELEGT)
940511 XOMA CORP. ; 940511 BEHRINGWERKE AKTIENGESELLSCHAFT ; 940511 BOEHRINGER MANNHEIM GMBH PATENTABTEILUNG
EP 194276 P 940901 EP NLR1 NL: OPPOSITION HAS BEEN FILED WITH THE EPO (NL: EUROPESE OCTROOIEN, WAARTEGEN OPPOSITIE IS INGESTELD)
XOMA CORP. + BEHRINGWERKE AG. + BOEHRINGER MANNHEIM GMBH
EP 194276 P 950131 EP EAL SE: EUROPEAN PATENT IN FORCE IN SWEDEN (SE: EUROPEISKT PATENT GAELLANDE I SVERIGE)
85904274.9
EP 194276 P 950705 EP R26 OPPOSITION FILED (CORRECTION) (EINSPRUCH EINGELEGT (KORR.))
940511 XOMA CORP. ; 940511 BEHRINGWERKE AKTIENGESELLSCHAFT ; 940511 BOEHRINGER MANNHEIM GMBH WERK PENZBERG ABT. GE-TB, DR. SCHREINER
EP 194276 P 950901 EP NLR1 NL: OPPOSITION HAS BEEN FILED WITH THE EPO (NL: EUROPESE OCTROOIEN, WAARTEGEN OPPOSITIE IS INGESTELD)
XOMA CORP.;BEHRINGWERKE AKTIENGESELLSCHAFT;BOEHRINGER MANNHEIM GMBH WERK PENZBERG ABT. GE-TB, DR. SCHREINE R
EP 194276 P 970924 EP RAP2 PATENT OWNER (CORRECTION) (PATENTINHABER (KORR.))
CELLTECH THERAPEUTICS LIMITED
EP 194276 P 971103 EP NLT2 NL: MODIFICATIONS (OF NAMES), TAKEN FROM THE EUROPEAN PATENT PATENT BULLETIN (NL: (NAAMS)WIJZIGINGEN, DIE ZIJN OVERGENOMEN UIT HET EP OCTROOIBLAD)
CELLTECH THERAPEUTICS LIMITED

GREAT BRITAIN (GB)
Patent (No,Kind,Date): GB 8422238 A0 841010
CHIMERIC PROTEINS (English)
Patent Assignee: NEUBERGER M S; RABBITTS T H
Priority (No,Kind,Date): GB 8422238 A 840903
Applic (No,Kind,Date): GB 8422238 A 840903
IPC: * C12N-015/00
Language of Document: English
Patent (No,Kind,Date): GB 8608827 A0 860514
CHIMERIC ANTIBODIES (English)
Patent Assignee: CELLTECH LTD
Priority (No,Kind,Date): GB 8422238 A 840903; WO 85GB392 W 850903
Applic (No,Kind,Date): GB 868827 A 860411
IPC: * C12N-015/00; A61K-039/395; C07K-003/18; C07K-015/00; C12N-005/00; C12P-021/00; G01N-033/563
CA Abstract No: * 105(05)036846F

Derwent WPI Acc No: * C 86-081635
Language of Document: English
Patent (No,Kind,Date): GB 2177096 A1 870114
PRODUCTION OF CHIMERIC ANTIBODIES (English)
Patent Assignee: CELLTECH LTD
Author (Inventor): NEUBERGER MICHAEL SAMUEL; RABBITTS TERENCE HOWARD
Priority (No,Kind,Date): WO 85GB392 A 850903; GB 8422238 A 840903
Applic (No,Kind,Date): GB 868827 A 860411
National Class: * C3H431 HB7M -; C3H642 HB7M -; C3H656 HB7M -; C3H675 HB7M -; C3H690 HB7M -; C3HB7M HB7M -; C6Y404 C3H -; C6Y404 HB7 -; C6Y404 HB7M -; C6Y501 C3H -; C6Y501 HB7 -; C6Y501 HB7M -; C6Y503 C3H -; C6Y503 HB7 -; C6Y503 HB7M -; U1S2419 C3H -; U1SC3H C3H -
IPC: * C12N-015/00; A61K-039/395; C07K-003/18; C07K-015/00; C12N-005/00; C12P-021/00; G01N-033/563
CA Abstract No: * 105(05)036846F
Derwent WPI Acc No: * C 86-081635
Language of Document: English
Patent (No,Kind,Date): GB 2177096 B2 890517
PRODUCTION OF CHIMERIC ANTIBODIES (English)
Patent Assignee: CELLTECH LTD (GB)
Author (Inventor): NEUBERGER MICHAEL SAMUEL; RABBITTS TERENCE HOWARD
Priority (No,Kind,Date): WO 85GB392 A 850903; GB 8422238 A 840903
Applic (No,Kind,Date): GB 868827 A 860411
National Class: * C3H HB7M HB7M; C3H H642 HB7M; C3H H656 HB7M; C3H H675 HB7M; C3H H690 HB7M; C6Y Y409; C6Y Y501; C6Y Y503; U1S S2419
IPC: * C12N-015/00; A61K-039/395; C07K-003/18; C07K-015/00; C12N-005/00; C12P-021/00; G01N-033/563
CA Abstract No: * 105(05)036846F
Derwent WPI Acc No: * C 86-081635
Language of Document: English

GREAT BRITAIN (GB)
Legal Status (No,Type,Date,Code,Text):
GB 2177096 P 840903 GB AA PRIORITY (PATENT)
GB 8422238 A 840903
GB 2177096 P 850903 GB AA PRIORITY (PATENT)
WO 85GB392 A 850903
GB 2177096 P 860411 GB AE APPLICATION DATA (APPL. DATA)

GB 868827 A 860411
GB 2177096 P 870114 GB A1 APPLICATION PUBLISHED
GB 2177096 P 890517 GB B2 PATENT GRANTED

JAPAN (JP)
Patent (No,Kind,Date): JP 62500352 T2 870219
Priority (No,Kind,Date): WO 85GB392 W 850903; GB 8422238 A 840903
Applic (No,Kind,Date): JP 85503940 A 850903
IPC: * C12P-021/00; A61K-039/395; C07H-021/04; C07K-015/12; C12N-005/00; C12N-015/00; G01N-033/577; C12R-001-91
Language of Document: Japanese
WORLD INTELLECTUAL PROPERTY ORGANIZATION, PCT (WO)

Patent (No,Kind,Date): WO 8601533 A1 860313
PRODUCTION OF CHIMERIC ANTIBODIES (English)
Patent Assignee: CELLTECH LTD (GB)
Author (Inventor): NEUBERGER MICHAEL SAMUEL (GB); RABBITTS TERENCE HOWARD (GB)
Priority (No,Kind,Date): GB 8422238 A 840903
Applic (No,Kind,Date): WO 85GB392 A 850903
Designated States: (National) GB; JP; US (Regional) AT; BE; CH; DE; FR; GB; IT; LU; NL; SE
Filing Details: WO 10000 With international search report
IPC: * C12N-015/00; C07K-015/00; A61K-039/395; C07K-003/18; C12N-005/00; C12P-021/00; G01N-033/563
CA Abstract No: ; 105(05)036846F
Derwent WPI Acc No: ; C 86-081635
Language of Document: English

WORLD INTELLECTUAL PROPERTY ORGANIZATION, PCT (WO)
Legal Status (No,Type,Date,Code,Text):

WO 8601533	P 840903	WO AA PRIORITY (PATENT) GB 8422238 A 840903
WO 8601533	P 850903	WO AE APPL. DATA WO 85GB392 A 850903
WO 8601533	P 860313	WO AK DESIGNATED STATES CITED IN A PUBLISHED APPL. WITH SEARCH REPORT GB JP US
WO 8601533	P 860313	WO AL DESIGNATED COUNTRIES FOR REGIONAL PATENTS CITED IN A PUBLISHED APPL. WITH SEARCH REPORT AT BE CH DE FR GB IT LU NL SE
WO 8601533	P 860313	WO A1 PUB. OF THE INTERNATIONAL APPL. WITH THE INTERNATIONAL SEARCH REPORT